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EXAMINER

SULLIVAN, DANIEL M

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/769,902

Applicant(s)

GOODMAN ET AL.

Examiner

Daniel M Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

This Office Action is a reply to the Paper filed 29 March 2004 in response to the Non-Final Office action mailed 29 December 2003. Claims 1-30 were considered in the 29 December Office Action. Claims 1-7, 9-11 and 13-29 were amended in the 29 March Paper. Claims 1-30 are pending and under consideration.

Response to Amendment

Claim Rejections - 35 USC § 112

Rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, as containing new matter is withdrawn.

Claims 1-12 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for reasons of record and herein below in the response to arguments.

Claims 1-30 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record and herein below in the response to arguments.

Claims 1-30 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement

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Rejection of claims 16, 17 and 19-21 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn.

Response to Arguments

Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for gene therapy in the First Office Action on the Merits, mailed 3 July 2002, and the rejection has been maintained through the 29 December Office Action.

In response to the *prima facie* case and arguments of record, Applicant has amended claim 1 and 9 such that they now recite, “A method of regulating the expression of an exogenous gene introduced into a subject by a gene therapy...” and “A method for regulating the expression of an exogenous gene introduced into a subject by a gene therapy...”, respectively. In the accompanying remarks, Applicant urges, “the claimed subject matter is not directed to establishing a gene therapy, but instead to regulating expression of an exogenous gene introduced by an extant gene therapy” (first full paragraph on page 12).

This argument has been fully considered but is not deemed persuasive. Applicant’s argument, as it is understood by the Examiner, is that the issue of enablement for gene therapy is not relevant to the claims because the claims are somehow limited to a method practiced in conjunction with an established, and therefore enabled gene therapy method. However, even if one is to assume, *arguendo*, that the claims are not directed to establishing a gene therapy, enablement for the method still requires enablement for gene therapy because the method is explicitly limited to being practiced in the context of gene therapy. A disclosure in an application, to be complete, must contain such description and details as to enable any person

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skilled in the art or science to which the invention pertains to make and use the invention *as of its filing date*. “[T]he filing date becomes a date of constructive reduction to practice in determining priority of invention and this should not be the case unless at that time, without waiting for subsequent disclosures, any person skilled in the art could practice the invention from the disclosure of the application. If information to be found only in subsequent publications is needed for such enablement, it cannot be said that the disclosure in the application evidences a completed invention.” *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). Even if, as applicant asserts, the claims only encompass the method practiced with an existing gene therapy, the method was not enabled at the time of filing because, for the reasons provided in previous Office Actions, gene therapy was not enabled at the time of filing. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement.

Claims 1-12 were further rejected on the grounds that the specification fails to enable the full scope of the vectors comprising electromagnetic response elements used in the claimed method. The scope of the vector encompassed by the amended claims is still beyond what is enabled by the specification for reasons set forth herein below regarding claims 13-30.

Claims 13-30 were rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claims because the disclosure while being enabling for an expression vector comprising a chimeric regulatory sequence comprising the 900 bp region of the c-myc promoter from -353 to -1257, relative to the transcriptional start site, fused to the first 111 base pairs upstream of the transcription initiation site of the HSP70 promoter and a method of regulating the expression of a nucleic acid in a cell *in vitro*, does not reasonably provide

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enablement for any promoter comprising at least one exogenous electromagnetic response element or a method of using the enabled promoter *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

With regard to practicing the claimed invention *in vivo*, the 29 December Office Action states, "Claims 22-30 are directed to a method for regulating expression of a nucleic acid in a cell using the electromagnetic field responsive promoter. According to the broadest reasonable interpretation, the claims encompass a method of regulating expression *in vitro* or *in vivo*. As the specification provides no asserted utility or guidance as to how the skilled artisan is to use the method *in vivo* other than gene therapy, the claims lack enablement for the method practiced *in vivo* for the reasons set forth in previous Office Actions and herein above" (bridging pages 7-8). Applicant's remarks do not address these grounds for rejection.

With regard to enablement for the broad scope of any promoter comprising at least one exogenous electromagnetic response element, Applicant has amended the claims such that the electromagnetic response element is limited to comprising the sequence nCTCTn.

In the accompanying remarks, Applicant takes particular exception to the Examiner's assertion that the teachings of Arnone *et al.* indicate that it is highly unlikely that the sequence nCTCTn would confer electromagnetic responsiveness to any promoter. Applicant notes that Arnone *et al.* does not discuss nCTCTn and Arnone *et al.* has no teaching with regard to EMRE's. Applicant requests that the Examiner state the location of the support in the Arnone *et al.* article.

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The statement referred to by Applicant actually reads, “[t]hus, Arnone *et al.* teaches that it is highly unlikely that a regulatory module could be defined by the binding of c-myc to the sequence nCTCTn, or that the presence of such a sequence would confer electromagnetic field responsiveness to any promoter” (page 9, emphasis added). The statement is a logical conclusion, based on the discussion of the teachings cited from Arnone *et al.* immediately preceding the statement, that the skilled artisan would not expect a four base sequence to define regulatory module of sufficient complexity to be capable of conferring electromagnetic field responsiveness to any promoter. It must be kept in mind that using the claimed invention according to the teachings of the specification requires that the promoter created by inserting the electromagnetic response elements be capable of responding to electromagnetic fields. The full extent of the teachings found in the art and the instant disclosure provides only that a promoter construct comprising a 900 base pair module from the c-myc promoter inserted upstream of the HSP70 heat shock responsive element is responsive to electromagnetic fields, and that electromagnetic field responsiveness of the HSP70 promoter is lost upon deletion of nCTCTn sequences therefrom. Based on these two findings and a leap of logic, Applicant has concluded that insertion of nCTCTn elements into promoters not having electromagnetic response elements will make them responsive to electromagnetic fields. However, the teachings of Arnone *et al.* and Lin *et al.* discussed in the previous Office Action call into question the predictability of Applicant’s leap of logic.

Applicant points out that Arnone *et al.* discusses multi-component “regulatory modules” which “contribute in various ways to the overall regulatory output” and asserts that this is not germane to the claim of an EMRE affecting expression and notes that the claimed subject matter

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is not incompatible with the concept of other regulatory elements also affecting expression.

Likewise, Applicant dismisses the teachings of Lin *et al.*, which was cited as evidence that the general complexity of regulatory modules taught by Arnone *et al.* is likely to apply to regulation of the electromagnetic field response, as discussing the overall regulatory output and in no way teaching against the effects of individual regulatory components such as an EMRE. This argument has been fully considered but is not deemed persuasive. Applicant's argument seems to be predicated on the notion that the sequence nCTCTn defines a functional EMRE. However, the unpredictability of this basic premise, which is evidenced by the teachings of Arnone *et al.* and Lin *et al.*, is precisely why the claims are not enabled. At the time of filing, the skilled artisan in possession of the formula nCTCTn=EMRE would have no idea what the identity of "n" must be to make the equation true. The skilled artisan would not expect that the sequence CTCT would function as an EMRE regardless of context and, outside of the context of a 900 base pair module from the c-myc promoter fused to the HSP70 heat shock responsive element, would not know what sequence in addition to CTCT would be required for operability. Therefore, the skilled artisan would have to engage in undue trial and error experimentation to identify the subject matter claimed.

Finally, Applicant argues that although some experimentation may be required to identify other promoters falling within the scope of the claims, the experimentation would be routine and therefore would not be undue. Applicant urges that one need only identify electromagnetic responsiveness in a promoter with an EMRE inserted to practice the claims. This argument has been fully considered but is not deemed persuasive because it fails to appreciate the tremendous scope of the subject matter encompassed by a promoter comprising an exogenous nCTCTn

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electromagnetic field response element and the likelihood that the vast majority of promoters having these structural limitations would not respond to electromagnetic fields. As described in detail in the previous Office Action and herein above, the guidance available to the skilled artisan as to the structural requirements for electromagnetic field responsiveness was extremely limited. Therefore, the skilled artisan seeking to practice the full scope of the claims would have to test many thousands of possible promoter configurations. Although the presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled (see *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414). *Atlas* also provides, “[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid” (page 414). In the instant case, the tremendous number of inoperative combinations within the scope of the claims would clearly force the skilled artisan to experiment unduly in order to practice the claimed invention.

Applicant’s arguments have been fully considered but are not deemed persuasive either individually or as a whole; therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Claims 1-30 were further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In response, Applicant has amended the claims such that they now recite that the EMRE’s comprise the sequence nCTCTn, which Applicant states is readily identifiable. Applicant further notes that a method of modifying a stretch of promoter DNA does not require a

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description of all existing DNAs and urges that the claims are not directed to DNA's, but merely a method of modifying certain promoters.

These arguments have been fully considered but are not deemed persuasive. First, Applicant's statements mischaracterize the claims. The claims are, in fact, directed to DNA's (*i.e.*, a vector) and methods of using DNA's comprising promoters regulatable by electromagnetic fields wherein the promoters are constructed by introducing an nCTCTn electromagnetic field response element into a promoter not having any electromagnetic field response elements. Therefore, adequate description of the claimed subject matter requires that the promoters themselves be described. None of the claims at issue are directed to a method of modifying certain promoters.

With regard to the sequence nCTCTn, for reasons stated in the previous Office Action and herein above, the skilled artisan would not expect an electromagnetic response element to be fully described by the sequence CTCT. Therefore, the sequence represented by "n", which is undefined, is critical to the function of the electromagnetic response element and must also be described. Other than a 900 base pair module from the c-myc promoter fused to the HSP70 heat shock responsive element, the specification provides no description of the promoter comprised by the claimed vector and used in the claimed method. Therefore, the skilled artisan could not possibly envision the promoter of the claims.

Applicant argues that one of ordinary skill in the art can readily identify whether a promoter contains EMRE's; however, as pointed out in the previous Office Action, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA

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itself. It is not sufficient to define DNA solely by its principal biological property (*i.e.*, it is an electromagnetic response element) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property” (page 14).

Finally, Applicant argues it is not necessary to fuse the c-myc and HSP70 promoters because the promoters can be electromagnetically responsive with nCTCTn sequences present. However, the portion of the specification cited to support this statement has to do with the HSP70 promoter comprising an endogenous electromagnetic response element. In contrast, the claimed invention requires that a promoter be constructed by introducing an electromagnetic field response element into a gene promoter not having any electromagnetic field response elements. The basis of the instant rejection is that the disclosure fails to describe an electromagnetic field response element that is capable of providing electromagnetic field responsiveness to a promoter not having any electromagnetic field response elements other than a 900 base pair module from the c-myc promoter, which is only demonstrated to be capable of conferring electromagnetic field responsiveness on the HSP70 heat shock responsive element. Therefore, the disclosure fails to provide descriptive support for the promoter of the claims beyond this scope.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking written description.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 7, 17, 20, 26 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The MPEP states, “[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” (MPEP § 2163.06). The MPEP further states, “[w]henver the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application” (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

In the instant case, the claims have been amended to recite that the electromagnetic response elements lie within some range which is now defined as relative to the transcription

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initiation site of the c-myc or HSP70 gene promoter. To support the new limitations, Applicant cites the second and third paragraphs on page 6 of the specification. However, the cited teachings state, “[t]he nCTCTn sequences may lie between about –230 and about –160 in the HSP70 gene promoter” and “[t]he nCTCTn sequences may lie between about –1257 and about –353 in the c-myc gene promoter.” The cited teachings do not explicitly state that the range is provided relative to the transcriptional start site and the skilled artisan would not assume that the limitation is inherent to the teaching because the +1 site within a gene is more frequently identified as the translational start site, rather than the transcriptional start site. Thus, the limitation to a range relative to the transcriptional start site within the c-myc or HSP70 genes is neither explicitly nor implicitly present in the originally filed disclosure, and the inclusion of the limitation in the claims constitutes new matter.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779.

The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER